## Literature review

# Childhood acute lymphoblastic leukemia

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### Introduction

The incidence of childhood cancers in Thailand is approximately 2 per 100,000 individuals. Each year, around 1,000 children under the age of fifteen are diagnosed with cancer.[1,2] Compared among Thai children, the number is nearly equal (about 3,000 children in 3 years).[3] Leukemia represents the most prevalent malignant neoplasm among pediatric patients, accounting for 38.1%, or roughly one-third of all childhood cancers.[3]

Leukemia originates from abnormal proliferation and differentiation of hematopoietic stem cells in the bone marrow. These aberrations can occur at any stage of cell division within the lymphoid or myeloid lineages. The presence of these abnormal cells disrupts the function of normal hematopoietic cells, potentially leading to anomalies in red blood cells, white blood cells, or platelets.[4] Leukemia is categorized into four types based on micropathology characteristics and disease progressions. These include acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), chronic myeloid leukemia, and chronic lymphocytic leukemia.[4] This article mainly focused on pediatric ALL.

### Incidence

Acute leukemia is more frequent than chronic leukemia in pediatric populations. Among these, ALL is more common than AML, as indicated in Table 1. In the US, the annual incidence of ALL is between 2,500 and 3,000 cases, in contrast to 500 cases of AML.[5,6] Moreover, a study by S. Wiangnon et al.,[3] conducted in Thailand from 2003 to 2005, reported 1,029 cases of ALL (approximately 514.5 cases yearly), compared with 328 cases of AML (164 cases yearly). The peak age for acute leukemia onset is between 2 and 5 years. Furthermore, patients with ALL are generally younger than those receiving a diagnosis of AML.[5,6]

### Etiology

The exact causes of acute leukemia remain largely unknown. However, several risk factors have been identified that are associated with developing this disease.[7,8] These include the categories listed below.

- **Age:** In children, the most common age group is 0-4 years, and followed by 5-9 years.[3]
- **Sex:** ALL is more common in boy than in girl. (age-standardized rate; ASRs 31.4 vs 24.2)[3]
- **Exposure to high levels of radiation:** This includes contact with radioactive substances.
- **Viral Infections:** Certain viral infections, such as HTLV-1, have been implicated.
- **Genetic Factors:** A notable risk in familial contexts has been reported. For instance, if one identical twin develops acute leukemia before the age of 5, the other twin has a 20% increased risk and the siblings have a fourfold greater risk compared with that in the general population. Most cases of leukemia do not develop from

**Table 1** Types of leukemia and their proportions in the pediatric population (adapted from the reference[4]).

| Type of leukemias | Prevalence in pediatric population (percent) |
|---|---|
| acute lymphoblastic leukemia | 80 |
| acute myeloid leukemia | 17 |
| chronic myeloid leukemia | 3 |
| chronic lymphocytic leukemia | Not found in children |

**Table 2** Genetic disorders related to elevating the risk of leukemia (adapted from the reference[7,8]).

| Genetic disorders related to elevate the risk of leukemia |
|---|
| Trisomy 21 |
| Fanconi anemia |
| Congenital agammaglobulinemia |
| Poland syndrome |
| Shwachman-Diamond syndrome |
| Ataxia telangiectasia |
| Li-Fraumeni syndrome (*p53* germline mutation) |
| Neurofibromatosis |
| Diamond–Blackfan anemia |
| Kostmann disease |
| Bloom syndrome |

an inherited genetic predisposition but from somatic genetic alteration. However, recent studies indicate a possible genetic linkage with inherited polymorphisms in genes such as *ARID5B* and *IKZF1*. Moreover, certain genetic disorders are known to elevate the risk of leukemia, as detailed in Table 2.

**Clinical characteristics**

Hematopoietic stem cells in the bone marrow are an important part that produces various blood cells including red blood cells, white blood cells, and platelets. Among acute leukemia patients, the abnormal blast cells are substituted for these normal cells and cannot develop into mature blood cells, combined with increased abnormal cells leading to the failure of producing normal blood cells. Therefore, patients with leukemia experience symptoms and signs related to bone marrow failure including chronic fatigue from decreased red blood cells or hemoglobin, fever or infections from reduced white blood cells, or abnormal bleeding from decreased platelets. These patients might experience bone pain from the uncontrolled expansion of abnormal cells. They might present a mediastinal mass (lump in the chest) and may experience respiratory symptoms such as dyspnea, shortness of breath or cardiovascular symptoms such as a swollen face and neck from compression. The other non-specific symptoms include loss of appetite or weight loss.

Physical examinations might find bleeding, fever, hemorrhage, or enlarged liver, spleen, and lymph nodes. For male patients whose cancer cells have spread to the testicles, a lump in the testicles can be detected. For patients whose cancer cells have spread to the nervous system or brain, cranial nerve palsy can be detected. However, although the patient did not present any central nervous system (CNS) sign or symptom, the physician must investigate cancer cells in cerebrospinal fluid (CSF) because this sanctuary area is the most common for extramedullary involvement.[9-11] These symptoms and signs are demonstrated in Table 3.

**Laboratory investigations**

Initial laboratory tests for patients suspected of leukemia typically include a complete blood count and peripheral blood smears. In most cases of acute leukemia, abnormal white blood cell count, low hemoglobin level, and thrombocytopenia are observed. The white blood cell count may vary, being normal, decreased, or increased. Microscopic examination of the blood cells often reveals the presence of leukemia cells, known as peripheral blasts. The microscopic examination of blood cells is crucial as it detects peripheral blasts and aids in differentiating between lymphoblastic and myeloid types of acute leukemia. This distinction is vital for planning initial treatment strategies before referring the patient for more specific therapies. The differing

**Table 3** Sign, symptoms, and investigations in acute leukemia patients (adapted from the reference[8,12]).

| Signs, symptoms, and investigations | Percent |
|---|---|
| Fever | 61 |
| Abnormal bleeding | 48 |
| Bone pain | 23 |
| Lymphadenopathy | 50 |
| Splenomegaly | 63 |
| Hepatosplenomegaly | 68 |
| White blood cells (cell/mm$^3$) | |
| Less than 10,000 | 53 |
| 10,000-50,000 | 30 |
| More than 50,000 | 17 |
| Hemoglobin (g/dL) | |
| Less than 7.0 | 43 |
| 7.0-11.0 | 45 |
| More than 11.0 | 12 |
| Platelets (/mm$^3$) | |
| Less than 20,000 | 28 |
| 20,000-100,000 | 47 |
| More than 100,000 | 25 |

**Table 4** Differentiating characteristics of lymphoblastic and myeloid leukemia cells by microscopic examination of blood cells (adapted from the reference[8]).

| Leukemic cell | Lymphoblast | Myeloblast |
|---|---|---|
| Size | Small to medium, varying | Large, same |
| Nuclear chromatin | Coarse | fine |
| Nucleolus | None or 1-2 | 1-4 and distinctive |
| Cytoplasm | Scanty | Increase |
| Auer rod | Not found | Might be found in 60-70% of cases |

characteristics of lymphoblastic and myeloid leukemia cells are detailed in Table 4.

Additional laboratory tests may be necessary to assess the side effects of acute leukemia. These include liver function tests (LFT), kidney function tests (blood urea nitrogen - BUN, and creatinine), coagulation studies, and tumor lysis laboratory assessments (including potassium, phosphorus, calcium, and uric acid levels). In cases of tumor lysis syndrome (TLS), increased levels of potassium, phosphorus, and uric acid, along with decreased calcium levels due to calcium binding with phosphorus and precipitating in tissues, are often observed.

Initial radiologic examinations, such as chest radiography, are essential for evaluating mediastinal masses among patients. This is particularly important in planning the administration of anesthesia for procedures like bone marrow aspiration, biopsy, and lumbar puncture, due to the increased risk of airway obstruction from mediastinal masses.[13-17]

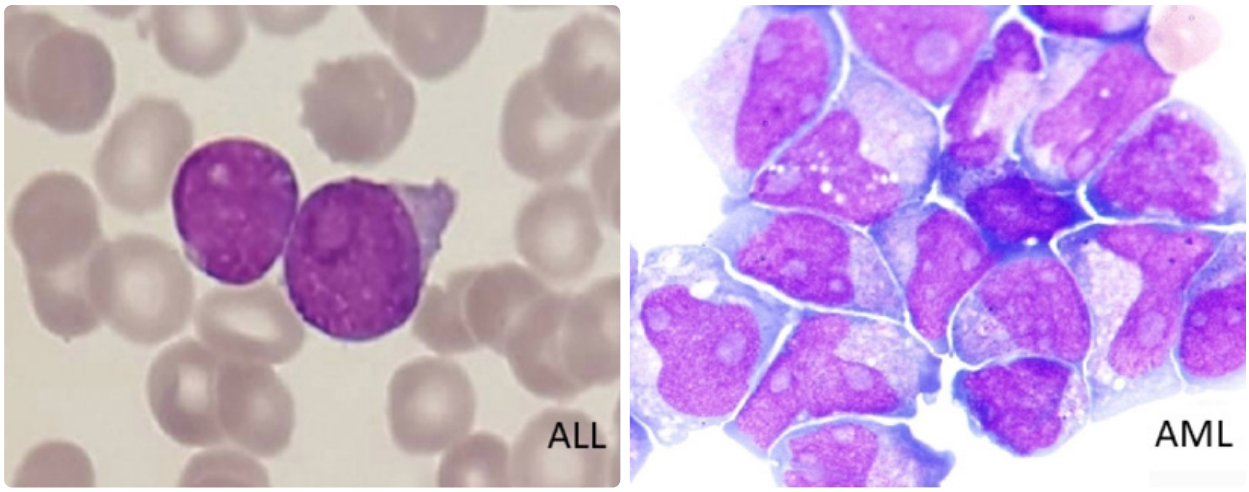


**Figure 1** Characteristics of acute leukemia cells in lymphoblastic (ALL) and myeloid (AML) types, as observed under a microscope.

**Diagnosis and classification**

The diagnosis and classification of acute leukemia are primarily established by examining cell characteristics in the bone marrow, as illustrated in Figure 1. A diagnosis of acute leukemia is generally confirmed when the proportion of cancer cells in the bone marrow exceeds 25% in ALL and 20% in AML. Additionally, immunophenotyping, or specialized immunological staining tests, are conducted on bone marrow examination to identify antigens specific to each type of cancer cell. Immunophenotyping is a conventional instrument to distinguish among the types of acute leukemia. Currently, testing for chromosomal and molecular genetic abnormalities is crucial for classifying, assessing risk levels, and determining the prognosis for each patient.[18-20]

The current classification of ALL adheres to the principles outlined in the 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Lymphoid, Myeloid, and Histiocytic/ Dendritic Neoplasms, 2022[21,22], as detailed in Table 5.

The degree of correlation between each antigen and the lineage under evaluation determines which lineage is assigned by immunophenotyping. An antigen's likelihood of reflecting a certain lineage increases with its similarity to the intensity and/or pattern of expression observed in the most similar normal population. Furthermore, the specificity of those antigens for lineage assignment is further enhanced by the display of a coordinated pattern of expression of numerous antigens from the same lineage, for example, simultaneous expression of CD19, CD22 and CD10 is more strongly associated with B lineage as opposed to each antigen on its own. Considering these ideas, the immunophenotypic standards that should be applied when attempting to ascribe a lineage to an individual when none is obvious have been updated in Table 6.[21,22]

**Treatment strategies in pediatric ALL**

The primary treatment for pediatric ALL is conventional chemotherapy. However, treatment protocols vary based on the disease's risk stratifications (risk-adapted therapy), depending on prognostic factors and the patient's response to treatment. Among pediatric ALL patients, the typical treatment duration is 2.5 to 3 years. It has been observed that pediatric ALL patients generally respond to treatments and exhibit better survival rates than AML.[23-24]

**Initial care before specific treatment:**

Providing primary care before specialized treatment is crucial for patient survival. This includes the items discussed below.

1. Fluid Administration[25-26]: Patients with newly diagnosed acute leukemia, particularly those with high initial white blood cell counts (leukocytosis or

**Table 5** The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours**:** Lymphoid, Myeloid, and Histiocytic**/**Dendritic Neoplasms (adapted from the reference[21,22]).

| |
|---|
| **Precursor B-cell neoplasms** |
| *B-cell lymphoblastic leukemias/lymphomas* |
| B-lymphoblastic leukemia/lymphoma, NOS |
| B-lymphoblastic leukemia/lymphoma with high hyperdiploidy |
| B-lymphoblastic leukemia/lymphoma with hypodiploidy |
| B-lymphoblastic leukemia/lymphoma with iAMP21 |
| B-lymphoblastic leukemia/lymphoma with *BCR::ABL1* fusion |
| B-lymphoblastic leukemia/lymphoma with *BCR::ABL1*-like features |
| B-lymphoblastic leukemia/lymphoma with *KMT2A* rearrangement |
| B-lymphoblastic leukemia/lymphoma with *ETV6::RUNX1* fusion |
| B-lymphoblastic leukemia/lymphoma with *ETV6::RUNX1*-like features |
| B-lymphoblastic leukemia/lymphoma with *TCF3::PBX1* fusion |
| B-lymphoblastic leukemia/lymphoma with *IGH::IL3* fusion |
| B-lymphoblastic leukemia/lymphoma with *TCF3::HLF* fusion |
| B-lymphoblastic leukemia/lymphoma with other defined genetic abnormalities |
| **Precursor T-cell neoplasms** |
| *T-lymphoblastic leukemia/lymphoma* |
| T-lymphoblastic leukemia/lymphoma, NOS |
| Early T-precursor lymphoblastic leukemia/lymphoma |
| **Acute leukemia of ambiguous lineage with defining genetic abnormalities** |
| Mixed-phenotype acute leukemia with *BCR::ABL1* fusion |
| Mixed-phenotype acute leukemia with *KMT2A* rearrangement |
| Acute leukemia of ambiguous lineage with other defined genetic alterations |
| Mixed-phenotype acute leukemia with *ZNF384* rearrangement |
| Acute leukemia of ambiguous lineage with *BCL11B* rearrangement |
| **Acute leukemia of ambiguous lineage, immunophenotypically defined** |
| Mixed-phenotype acute leukemia, B/myeloid |
| Mixed-phenotype acute leukemia, T/myeloid |
| Mixed-phenotype acute leukemia, rare types |
| Acute leukemia of ambiguous lineage, not otherwise specified |
| Acute undifferentiated leukemia |

hyperleukocytosis, with counts exceeding 100,000 cells/mm$^3$) are at risk of developing TLS. These patients, often experiencing dehydration due to anorexia, should receive aggressive hydration, recommended at 2,500 to 3,000 mL/m$^2$/day, except in cases with a risk of fluid overload, e.g., patients with a mediastinal mass. The goal is to achieve a urine output of 80 to 100 mL/m$^2$/hour, or 60-80% of the fluid intake. Diuretics may be considered when urine output is lower than expected and no urinary tract obstruction is found. Aggressive hydration is also indicated when administering certain chemotherapy drugs like high-dose methotrexate.[27]

2. Maintaining Electrolyte Balance[28-32]: A risk of TLS exists at the initial diagnosis of acute leukemia. While no universally accepted diagnostic criteria are available for TLS, the most referenced are the Cairo-Bishop criteria[33]. TLS can be classified as laboratory tumor lysis syndrome (LTLS) based on lab results and clinical tumor lysis syndrome (CTLS) based on clinical features. LTLS is diagnosed when a patient exhibits significant changes

**Table 6** Lineage assignment criteria for mixed-phenotype acute leukemia (adapted from Reference [21,22]).

| Lineages | Criterion |
|---|---|
| **B lineage** | |
| CD19 strong[1] | 1 or more also strongly expressed: CD10, CD22, or CD79a[3] |
| or, | |
| CD19 weak[2] | 2 or more also strongly expressed: CD10, CD22, or CD79a[3] |
| **T lineage** | |
| CD3 (cytoplasmic or surface)[4] | Intensity in part exceeds 50% of mature T-cells level by flow cytometry<br>or,<br>Immunocytochemistry positive with non-zeta chain reagent |

[1]CD19 intensity in part exceeds 50% of normal B cell progenitor by flow cytometry; [2]CD19 intensity does not exceed 50% of normal B cell progenitor by flow cytometry; [3]Provided T lineage not under consideration, otherwise cannot use CD79a; [4]Using anti-CD3 epsilon chain antibody

in electrolyte levels, either exceeding or falling below specific criteria or showing a change of more than 25% from baseline levels. At least two such abnormalities within three days before treatment and up to 7 days after treatment initiation are required for diagnosis.

LTLS may include elevated levels of potassium, uric acid, and phosphorus and decreased calcium levels due to the release of intracellular contents from lysed cancer cells. Consequently, fluids administered to patients should not contain potassium. In cases of hyperkalemia with ECG changes, intravenous calcium gluconate should be considered. When the ECG is normal, treatment may involve shifting potassium back to cells using insulin with intravenous glucose, beta-agonists, or sodium bicarbonate, and removing potassium from the body using diuretics, potassium-binding resins, or dialysis. For mild hyperphosphatemia without symptoms, phosphorus-binding medications or avoidance of phosphorus-containing fluids may be sufficient. In severe cases, dialysis may be required. For hyperuricemia, uric acid-lowering medications like allopurinol are recommended, with dosages of 100 mg/m$^2$/day or 10 mg/kg/day, not exceeding 800 mg daily. In asymptomatic hypocalcemia, calcium levels typically normalize with the resolution of TLS; thus, intravenous calcium is not advised unless the patient is symptomatic.

3. Blood and Blood Component Transfusion: Transfusions are indicated for patients with ALL. However, in cases of extreme leukocytosis and hyperviscosity risk, red cell transfusions should be considered with caution to avoid aggravated blood viscosity and potential complications like thrombosis or hemorrhage in the brain and lungs. Platelets and plasma may be administered to correct thrombocytopenia and coagulopathy, reducing the risk of hemorrhagic complications.

4. Infection Management: Among patients presenting fever or suspected infection, hemoculture should be obtained, and empiric antibiotic therapy initiated to cover both gram-positive and gram-negative bacteria. Once culture results are available, antibiotic therapy can be adjusted accordingly. For fever management, acetaminophen is recommended, while nonsteroidal anti-inflammatory drugs (NSAIDs) should be avoided due to their potential to impair platelet function and increase bleeding risk.[34-35]

**Treatment guidelines for pediatric ALL:**

Currently, the treatment of pediatric patients with ALL is stratified based on the disease's risk level (risk-adapted therapy).[36-38] The risk stratification is the disease-based prognostic factor, and is classified in the protocol as

"standard", "high" and "very high risk" for pediatric ALL. The criteria were divided into clinical criteria and molecular criteria. All criteria are based on mainly prognostic factors consisting of age at diagnosis, initial white blood cell count, immunophenotypes, cytogenetic abnormalities, CNS involvement, minimal residual disease, and any other specified status as Down syndrome, testicular involvement, and steroid pretreatment.

The disease-based risk stratification, intensive chemotherapies, CNS-directed prophylaxis and treatment were implemented according to the national pediatric ALL protocol (Table 7). Patients classified as low risk receive treatment tailored to minimize chemotherapy toxicity, while those in the high-risk categories are administered higher intense chemotherapy doses, aiming for complete eradication of leukemic cells.

Typically, the treatment regimen for pediatric ALL encompasses three phases: 1) Remission Induction Therapy, 2) Postinduction (Consolidation/Intensification) Therapy and 3) Maintenance Therapy. All patients undergo CNS-directed therapy although they present no sign, symptom or positive blast cell in CSF cytocentrifuge. CNS-directed therapy involves administering chemotherapy drugs intrathecally and may include methotrexate alone or combined with cytarabine and hydrocortisone (triple intrathecal chemotherapies). This strategy is designed to prevent leukemia from spreading to the CNS or to treat existing CNS involvement at diagnosis.[39]

**Chemotherapy regimens in pediatric ALL**

The primary chemotherapeutic agents used during remission induction include vincristine, prednisolone and L-asparaginase. For standard-risk patients, this regimen constitutes a three-drug induction therapy. In high-risk and very high-risk patients, doxorubicin is added, forming a four-drug induction therapy. Using this risk-based treatment approach, the rate of achieving complete remission after remission induction therapy reaches approximately 95%. During the postinduction (consolidation/intensification) phase, standard risk patients undergo consolidation, interim maintenance-I

**Table 7** Risk stratification in pediatric ALL according to the Thai Pediatric Oncology Group (ThaiPOG).

| Standard risk | High risk | Very high risk |
|---|---|---|
| | **Clinical criteria** | |
| ● Pre-B ALL<br>- age 1-9 years<br>- WBC < 50,000 cell/mm$^3$<br>● Down syndrome | ● T-ALL<br>● Pre-B ALL<br>- age 10-13 years<br>- WBC ≥ 50,000 cell/mm$^3$<br>● Testicular disease<br>● Steroid pretreatment | ● Pre-B ALL<br>- age ≥ 14 years<br>● CNS-3*<br>● Induction failure (lymphoblasts ≥ 5% in BM at day 29$^{th}$) |
| | **Molecular criteria (optional)** | |
| ● Day 29 BM MRD < 0.01%<br>● No unfavorable molecular feature | ● Day 29 BM MRD ≥ 0.01% with favorable cytogenetic: *ETV-6/RUNX-1* or double trisomy 4, 10 | ● Day 29 BM MRD ≥ 0.01% with no favorable cytogenetic<br>● Unfavorable molecular feature<br>o iAMP 21<br>o *MLL* (*KMT2A*) rearrangement<br>o Hypodipliody (<44 chromosome or DNA index <0.81)<br>o Ph-chromosome (follow Ph-ALL protocol) |

*CNS-3 status is defined by the presence of 5 or more white blood cells/mm$^3$ in the CSF cytocentrifuge, accompanied by the detection of lymphoblast cells.

and delayed intensification. High-risk patients receive augmented versions of these phases, while very high-risk patients additionally undergo interim maintenance II. The final stage of treatment for pediatric patients with ALL involves maintenance therapy, primarily using 6-mercaptopurine and oral methotrexate. The dosage is adjusted based on the absolute neutrophil count (ANC) and platelet levels, aiming to maintain an ANC of 500 to 1500 cells/$mm^3$ and platelet counts above 50,000 to 75,000/$mm^3$. In addition to these medications, patients periodically receive vincristine and corticosteroids every one to three months.[36-39]

## Conclusion

The survival rate for patients with ALL, particularly among younger patients, has significantly improved compared with that of the past. This success is attributed to effective current treatments, appropriate supportive care, rapid diagnosis, and proper initial management before referral to oncology specialists. Ongoing research and development in leukemia treatment continue to focus on enhancing survival rates for this patient group.

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